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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/687,281	10/13/2000	Hyun Kim	GI 5387	9127

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FINNEGAN HENDERSON FARABOW GARRETT & DUNNER
1300 I STREET N.W.
WASHINGTON, DC 20005-3315

EXAMINER	
HARLE, JENNIFER I	
ART UNIT	PAPER NUMBER
1654	

DATE MAILED: 03/31/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/687,281	KIM ET AL.	
	Examiner	Art Unit	
	Jennifer I. Harle	1654	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 March 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-7 and 11-37* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-7 and 11-37* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-7, and 11-37 are pending. All previous Office Actions are incorporated by reference.

Allowable Subject Matter

1. Claims 14, 16 and 28-37 are allowed because they have been rewritten in independent form, including all of the limitation of the base claim and any intervening claims.

The reasons for allowance was previously set forth in the prior Office Action and is set forth again below:

Claims 14, 16 and 28-37 require that the hyaluronic acid ester is Hyaff11p65. This ester does not appear to have been known in the art prior to the instant disclosure, see Campoccia, et al. (1998) and Radice, et al. (US 6,6699,471), and was not disclosed in a publication until WO 03/099992 (all previously cited). Given that the instant disclosure provides evidence of the advantage of this ester over other known Hyaff11 esters disclosed in Valentini, a rejection as obvious under 103 would not be sustainable and was not made. While della Valle, et al. (US 4,581,521) discloses methods of preparing various full and partial hyaluronic acid ester including benzyls used in Hyaff11, they do not explicitly disclose or reasonably suggest this particular ester or its advantages as instantly disclosed.

Claim Rejections - 35 USC § 103

2. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-5, 7 and 11-13 remain rejected and new claims 17-18 and 20-27 are rejected under 35 U.S.C. 103(a) as being unpatentable over Valentini, et al. (US 5,939,974) in view of Pheulpin (US 3,955,719), Langen, et al. (US 4,784,055) and Phillips, et al. (US 4,758,233).

3. Applicants' argue that the 35 U.S.C. 103 (a) rejection as obvious over Valentini in view in view of Pheulpin, Langen, and Phillips should not be persuasive because evidence submitted in the form of the Second Declaration made by Dr. Hyun Kim has demonstrated that the substance in the Valentini patent cannot be injected through the skin as required by the pending claims despite the Examiner's arguments to the contrary. Applicants' arguments are two-fold: 1) the Valentini references only teaches high levels of pore formers in the intermediate composition that is uninjectable because the composition comprises a thick slurry of hyaluronic acid ester, NACL and solvent that will not physically fit through a needle for injection through the skin of a patient because a phenomenon known as filter pressing will occur, i.e. the pressure of the syringe will cause the phases to separate, and the only material that will come out of the needle will be the solvent and the hyaluronic acid, BMPs, and pore former will precipitate and remain inside the syringe barrel and 2) the NaCl (or any other suitable pore former) are so high in the intermediate composition that it is unacceptable for pharmaceutical uses, i.e. they are superphysiological and if administered will cause tissue damage by altering the transport of ions into and out of cells, resulting in inflammation, apoptosis and cell toxicity if inserted into a patient. The Second Declaration of Dr. Hyun Kim under 37 CFR 1.132 filed March 17, 2005 is insufficient to overcome the rejection of claims 1-7, 11-13, 17-27 based upon the 35 U.S.C. 103 (a) rejection as obvious over Valentini in view in view of Pheulpin, Langen, and Phillips as set forth in the last Office action because: the Declaration merely sets forth statements that are not

supported by any factual evidence. The first reason that the composition will not be injectable because it is a thick slurry that will not physically fit through a needle for injection through the skin of a patient has not been substantiated. In the first instance, Applicants' state that the slurry comprises NaCl, however, the pore forming agent according to the patent may be "any of a variety of materials depending on the particular selection of the solvent and non-solvent." See col. 6, lines 4-8. Thus, there is not proof that the composition is of a slurry that is "thick." Additionally, the patent discloses that the porous scaffolds of the invention can be fabricated to any size or shape and can be produced to virtually any desired predetermine pore size depending upon the application, i.e. pore size is not an issue. See col. 2, lines 7-10. Further, Applicants' statement that the "thick slurry" will not fit through a needle for injection through the skin of a patient is not backed by any factual proof. Needles come in a wide variety of gauges and can vary depending upon the use and the patient. Applicants are limited by neither in their claims. Nor have they shown that the pressure of all gauges of syringes that can be utilized on all patients will cause the phases, i.e. all combinations of pore forming agents hyaluronic acid esters, and solvents to separate, leaving only the solvent. Just because a large bore needle is involved does not mean that the substance cannot be injected through the skin.

The second reason that the levels of NaCl (or any other suitable pore former) are so high in the intermediate composition that they are unacceptable for pharmaceutical uses are unsubstantiated by any evidence. Again, Applicants' state that the slurry comprises NaCl, however, the pore forming agent according to the patent may be "any of a variety of materials depending on the particular selection of the solvent and non-solvent." See col. 6, lines 4-8. Applicants' have not provided any factual evidence that any pore formers in the intermediate

composition are superphysiological to patients, let alone the plethora of pore forming agents that could be utilized depending upon the solvent as disclosed by the patent. Applicant's statements are conclusory and self-serving without any supporting documentation or evidence. Applicants do not even point to sections of the patent that would demonstrate supersphysiological conditions.

Thus, the Examiner has noted the deficiencies of the Kim declarations in this Office Action and the Final Office Action. Applicants arguments that Valentini does not teach or suggest compositions meeting all of the limitations of the claims, misconstrues a 103(a) rejection based upon the Kim Declarations is insufficient for the reasons set forth. The examiner has not set forth an unsupported statement that he does not agree with Dr. Kim's Declaration but has repeatedly set forth a reasoned analysis as to the deficiency of the Declarations. The examiner has respectfully disagreed with Dr. Kim's presentation that the size and presence of the pore formers of the intermediate composition render that composition uninjectable for the reasons set forth above and set forth previously. Again the specific reference in Dr. Kim's First Declaration to the liquid intermediate in col. 8 Table 1 only speaks to the pore former NaCl and is the preferred pore former and does not speak to whether the NaCl retain is pore size in the slurry, i.e. when the paste was made. Additionally, if you change the solvent and use a hydrogen instead of a soluble crystal, which is also taught, your paste may not have the same problems, as you are sieving your paste to obtain the size of microspheres you want, i.e. as previously set forth size is determinable based upon need.

Applicants further argue that there is no motivation to make the pore formers in Valentini smaller so that they can be injectable and that Valentini never intended that the intermediate be

used in this fashion. However, this argument is not found persuasive for the reasons set forth previously and above. The intermediate is injectable, whether so intentioned or not and the one preferred example does not outweigh the overall teaching of the patent itself.

The instant claims are drawn to a composition . As previously noted, the scaffolding is formed from mixed solution by drying from the wet state, preferably by lyophilization without freezing (col. 7, lines 22-24). Thus, it is clear that prior to drying, Valentini discloses a solution that meets the limitations of the instant claims. The same preferred hyaluronic acid esters - HYAFF®, the same pore-forming agents, the same tricalcium phosphate and several of the same BMPs, and the same solubilizing organic solvents are explicitly recited as being parts of this composition. There is no indication that the solutions are not injectable, just that it is preferred tot dry the solutions to form an implantable porous scaffold.

Moreover, Valentini discloses that the preferred hyaluronic derivative is 100% esterified hyaluronic acid-benylcovalent conjugates sold under the trade name HYAFF, thus claims 22-27 are rejected as disclosed by Valentini. Pheulpin, Langen and Phillips describe devices for the injection of pastes and liquids, i.e. Pheulipin for injection of pastes into dental cavities, Langen pastes into a meat, and Phillips injection of a medicament in the form of a cream or paste, i.e. through skin into muscle.

As per claims 6, 15 and 19, Applicants' argue that Wozney does not teach or suggest injectable hyaluronic acid esters, which are recited by the current claims. The examiner agrees that Wozeny does not teach hyaluronic acid esters but rather teaches hyaluronic acid in a pharmaceutical formulation with BMP-7 and BMP-12 in a syringe for injection. However, Valentini discloses that HYAFF-11 hyaluronic acid ester is preferable in vivo because it prevents

fast enzymatic degradation and degrades slowly in concert with new tissue formation. Thus, Wozeny was cited under 103(a) because it illustrates that in combination with Valentini, one would be motivated to use BMPs and OP-1 in injectable solutions containing an injectable hyaluronic acid ester. Thus, Applicants arguments of March 17, 2005 have been fully considered but not found persuasive.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jennifer I. Harle whose telephone number is (571) 272-2763. The examiner can normally be reached on Monday through Thursday, 6:30 am to 5:00 pm,.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Bruce Campell can be reached on (571) 272-0974. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Jennifer I. Harle
Examiner
Art Unit 1654

March 28, 2005